REMARKS

Reconsideration and withdrawal of the rejections of this application and consideration and entry of this paper are respectfully requested in view of the amendments and remarks herein, which place the application in condition for allowance.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 25, 27-32, and 34-44, and 47-48 are now pending in the present application. Claims 45 and 46 are cancelled without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Claims 25, 28, 29, 34, and 43 have been amended. Claims 47 and 48 are new.

Claims 28 and 29 have been amended to address informalities, and claims 34 and 43 have been amended to clarify certain structural cooperative relationships of elements recited therein. In addition, claims 25 and 34 have been amended to recite that the conditionally replicative adenovirus subtype 5 comprises a deletion ranging from nucleotides 324-488 of its genome. Support for this amendment can be found, *inter alia*, in Example 13 and Figure 23 of the instant specification. New claims 47 and 48 are supported by claims 34 and 43, respectively, from which they depend. No new matter has been introduced, nor is any new issue presented by these amendments and additions.

It is respectfully submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE RESTRICTION REQUIREMENT IS NOTED

The Office Action alleges that newly submitted claims 45 and 46 are directed to an invention that is independent or distinct from the invention originally claimed. Claims 45 and 46 allegedly materially differ in design to and do not encompass overlapping subject matter with the originally presented invention in that they involve complexing a bifunctional ligand to an adenovirus to change its tropism but not the tropism of its progeny whereas the originally

presented invention involves a genetic alteration to the fiber protein to alter its tropism and that of its progeny.

Although Applicants disagree, in the interest of expediting prosecution, claims 45 and 46 have been cancelled.

III. INFORMATION DISCLOSURE STATEMENT

Applicants thank the Examiner for noting that copies of documents AR and AT were not provided with the Information Disclosure Statement filed September 28, 2006. A Supplemental Information Disclosure Statement with copies of documents AR and AT and Form SB/08 citing same will accordingly be filed.

IV. THE CLAIM OBJECTIONS ARE OVERCOME

Applicants thank the Examiner for pointing out the informality, "claim25", in claim 28. Claim 28 has accordingly been corrected to recite "claim 25".

V. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH ARE OVERCOME

Claims 35-39 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims are alleged to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

Claims 35-39 are directed to a method of reducing tumor burden in a subject by administration of a modified conditionally replicative adenovirus subtype 5 that comprises and expresses a nucleotide sequence encoding the fiber domain from an adenovirus subtype 3 and comprises a promoter from a gene encoding "prostate specific antigen, carcinoembryonic antigen, secretory leukoprotease inhibitor, alpha-fetoprotein, vascular endothelial growth factor, CXCR4 or survivin". The Examiner contends that claims 35-39 contain impermissible new matter because of the recitation of promoters from genes other than VEGF.

Contrary to the Examiner's assertion, the specification provides support for these elements of the claims. In particular, Applicants respectfully draw the Examiner's attention to

paragraph 0072 of the application as published, which provides that early genes of adenoviruses may be conditionally regulated "by means consisting of a tissue-specific promoter operably linked to an early gene" and that "[r]epresentative tissue-specific promoters are derived from genes encoding proteins such as…Carcinoembronic antigen (CEA), secretory leukoprotease inhibitor (SLPI), alpha-fetoprotein (AFP), vascular endothelial growth factor, CXCR4 or survivin". [Emphasis added]. As noted in paragraph 0086 of the application as published, the examples are illustrative of certain embodiments of the invention, and as such, Example 13 is illustrative only of one embodiment of the invention. As provided in the specification, other promoters besides the VEGF promoter may be employed in the construction and use of conditionally replicative adenoviruses.

Accordingly, reconsideration and withdrawal of the rejection of claims 35-39 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Similar to claims 35-39 above, the Examiner contends that claims 43 and 44 contain impermissible new matter because of the recitation of promoters from genes other than CXCR4 and survivin. As similarly discussed above, the specification provides support for these elements of claims 43 and 44 (e.g., see paragraph 0076 of the application as published). Applicants point out that Example 14 is illustrative only of one embodiment of the invention. The specification provides that other promoters may be employed besides the CXCR4 or survivin promoters in the construction and use of conditionally replicative adenoviruses.

Accordingly, reconsideration and withdrawal of the rejection of claims 43-44 under 35 U.S.C. § 112 is respectfully requested.

VI. THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH ARE OVERCOME

Claims 34-44 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 34-44 are rejected as incomplete for omitting essential structural cooperative relationships of elements.

In accordance with the Examiner's suggestion, claims 34 and 43 have been amended to indicate that the fiber protein of the CRAd is a chimeric fiber protein comprising the hAd3 or the

canine adenovirus type 2 fiber knob domain, respectively, and that the CRAd comprises and expresses a nucleotide sequence encoding the chimeric fiber protein.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-44 under 35 U.S.C. §112, second paragraph is respectfully requested.

Claims 34-44 are further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Claims 34-44 are rejected as incomplete for omitting essential structural cooperative relationships of elements.

As suggested by the Examiner, claims 34 and 43 have been amended to clarify that the E1A promoter is replaced with the recited promoter region.

Accordingly, reconsideration and withdrawal of the rejection of claims 34-44 under 35 U.S.C. §112, second paragraph is respectfully requested.

VII. THE REJECTIONS UNDER 35 U.S.C. § 102 ARE OVERCOME

Claims 25, 28, 29, 34, 35, and 39 are rejected under 35 U.S.C. §102(a) as being anticipated by Takayama et al. Mol. Ther. 7 (5, Part2):S420, abstract 1089, May 2003 (hereinafter "Takayama (abstract 1089)"), as evidenced by Curiel et al. (WO 00/67576).

Claims 25, 26, 28, and 31 are rejected under 35 U.S.C. §102(b) as being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Res. Ann. Meet. 43: 662-663, Abstract 3287, March 2002)(hereinafter "Curiel (abstract 3287)"), as evidenced by Curiel, et al. (WO 00/67576) (hereinafter "Curiel (WO 00/67576)").

Applicants respectfully traverse the rejections.

Initially, it is respectfully pointed out that for a Section 102 rejection to stand, the single prior art reference must contain all of the elements of the claimed invention, *see Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987), and, the single prior art reference must contain an enabling disclosure, *see Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the references relied upon by the Office Action do not anticipate Applicants' invention.

Claims 25, 28, 29, 34, 35, and 39 are not anticipated by
Takayama et al. Mol. Ther. 7 (5, Part 2):S420, abstract 1089, May 2003

Claims 25, 28, 29, 34, 35, and 39 are rejected under 35 U.S.C. §102 (a) as allegedly being anticipated by Takayama et al. Mol. Ther. 7 (5, Part 2):S420, abstract 1089, May 2003 (hereinafter "Takayama (abstract 1089)") as evidenced by Curiel et al., WO 00/67576 (hereinafter "Curiel (WO 00/67576)"). Applicants respectfully traverse this rejection as applied to the claims as amended.

As amended, claims 25 and 34 (and by dependency, claims 28, 29, 35, and 39) recite a conditionally replicative adenovirus subtype 5, which comprises, *inter alia*, a deletion ranging from nucleotides 324-488 in the adenoviral subtype 5 genome. Takayama (abstract 1089) is silent on the type of adenovirus that was modified to express the knob domain of Ad3 and fails to teach a CRAd comprising a deletion ranging from nucleotides 324-488 of its genome.

Curiel (WO 00/67576) does not cure this defect. As with Takayama (abstract 1089), Curiel (WO 00/67576) does not teach a CRAd subtype 5 comprising a deletion ranging from nucleotides 324-488 of its genome.

As such, Takayama (abstract 1089) as evidenced by Curiel (WO 00/67576) does not teach every element recited in the pending claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a) is respectfully requested.

Claims 25, 26, 28, and 31 are not anticipated by Curiel, D.T.
(Proc. Amer. Assoc. Cancer Re. Ann. Meet. 43:662-663, abstract 3287, March 2002)

Claims 25, 26, 28, and 31 are rejected under 35 U.S.C. §102 (b) as allegedly being anticipated by Curiel, D.T. (Proc. Amer. Assoc. Cancer Re. Ann. Meet. 43:662-663, abstract 3287, March 2002) (hereinafter "Curiel (abstract 3287)") as evidenced by Curiel (WO 00/67576). Applicants respectfully traverse this rejection as applied to the claims as amended.

With respect to claim 26, the rejection is moot since claim 26 was cancelled earlier.

As amended, claim 25 (and by dependency, claims 28 and 31) recites a conditionally replicative adenovirus subtype 5, which comprises, *inter alia*, a deletion ranging from

nucleotides 324-488 in the adenoviral subtype 5 genome. Curiel (abstract 3287) is silent on the type of adenovirus that was modified and fails to teach a CRAd comprising a deletion ranging from nucleotides 324-488 of its genome.

Curiel (WO 00/67576) does not cure this defect. As with Curiel (abstract 3287), Curiel (WO 00/67576) does not teach a CRAd subtype 5 comprising a deletion ranging from nucleotides 324-488 of its genome.

As such, Curiel (abstract 3287) as evidenced by Curiel (WO 00/67576) does not teach every element recited in the pending claims. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 (b) is respectfully requested.

VIII. THE REJECTIONS UNDER 35 U.S.C. § 103 ARE OVERCOME

Claims 25, 27, 30-32, 34, and 39-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Takayama (Abstract 1089), in view of Curiel (WO 00/67576).

Claims 25, 27, 30-32, 34, and 39-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Curiel (Abstract 3287) in view of Curiel (WO 00/67576).

Claims 25 and 27-32 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Molnar-Kimber, WO 01/23004 (hereinafter "Molnar-Kimber") in view of Curiel (WO 00/67576).

Claims 36-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Takayama (Abstract 1089), as evidenced by Curiel (WO 00/67576), as applied to claims 25, 28, 29, 34, 35, and 39 above, and further in view of Takayama et al., Mol. Ther. 5 (5, Part 2):S268, Abstract 821, May 2002 (hereinafter "Takayama (Abstract 821)").

Claims 35-38 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Curiel (Abstract 3287) in view of Curiel (WO 00/67576), as applied to claims 25, 27, 30-32, 34, and 39-42 above, and further in view of Takayama (Abstract 821).

Applicants respectfully traverse these rejections as applied to the claims as amended. The cited references do not render the instant invention obvious.

Applicants respectfully point out that establishing a *prima facie* case of obviousness requires that the prior art references teach or suggest all the claim limitations. MPEP 2143. "To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

As amended, claims 25 and 34 (and by dependency, claims 27-32, and 35-42) recite a conditionally replicative adenovirus subtype 5, which comprises, *inter alia*, a deletion ranging from nucleotides 324-488 in the adenoviral subtype 5 genome. None of the cited references, either alone or in any combination, teach or suggest this element recited in the pending claims. At best, Molnar-Kimber pertains to E1A promoter deletions of nucleotides 431 to 555 of the adenoviral genome depicted in GenBank, Accession No. M73260 (see page 28, last two paragraphs).

Applicants remind the Examiner that it is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicants' structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office.

For the foregoing reasons, the cited references, either alone or in any combination, do not render the pending claims *prima facie* obvious. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

IX. THE DOUBLE PATENTING REJECTION IS OVERCOME

Claims 25, 27-32, and 34-42 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-3 and 9-12 of U.S. Patent No. 6,824,771 in view of Curiel (WO 00/67576), Takayama (Abstract 1089), and Takayama (Abstract 821). Applicants respectfully traverse this rejection.

As amended, claims 25 and 34 (and by dependency, claims 27-32 and 35-42) recite a conditionally replicative adenovirus subtype 5, which comprises, *inter alia*, a deletion ranging from nucleotides 324-488 in the adenoviral subtype 5 genome. None of the cited references teach or suggest this element of the pending claims.

Applicants nonetheless reiterate that the issue of whether there is indeed double patenting is contingent upon whether the remarks herewith are indeed considered and entered; and, if so, whether the Examiner believes there is overlap with claims ultimately allowed in the application. If, upon agreement as to allowable subject matter, it is believed that there is still a double patenting issue, a Terminal Disclaimer as to U.S. Patent No. 6,824,771 will be filed for the purposes of expediting prosecution.

Applicants note the Examiner's contention that the rejection will not be held in abeyance. Accordingly, reconsideration and withdrawal of the double patenting rejection is respectfully requested.

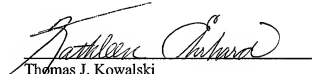
REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, an interview with the Examiner is respectfully requested, and the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

CONCLUSION

In view of the foregoing remarks and amendments, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,
FROMMER LAWRENCE & HAUG LLP

By: 

Thomas J. Kowalski
Reg. No. 32,147
Deborah L. Lu
Reg. No. 50,940
Kathleen N. Ehrhard
Reg. No. 55,144
Telephone: (212) 588-0800
Facsimile: (212) 588-0500